Biomarkers in the Psychotherapeutic Relationship: The Role of Physiology, Neurobiology, and Biological Correlates of E.M.P.A.T.H.Y.

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Emerging biomarker research could powerfully influence the practice of psychotherapy, a standard treatment that is as strongly rooted in brain plasticity as are psychopharmacologic interventions. Psychotherapy is associated with measurable changes in central and peripheral neurophysiology. These markers could be harnessed to aid informed, personalized recommendations for specific psychosocial treatments, to guide a course of treatment, and to predict treatment outcomes, in lieu of relying on costly, trial-and-error approaches. Psychotherapy and empathy research also demonstrate that the patient-doctor relationship has important neurophysiological correlates that can be salient to treatment outcomes, as illustrated in a case example. These correlates include autonomic nervous system arousal manifested by heart rate, respiration rate, muscle tension, and galvanic skin resistance; electroencephalography; and brain-imaging markers. While additional biomarker research is unfolding, there are specific neurobiologically based clinical and subclinical observations, organized by using the E.M.P.A.T.H.Y. mnemonic, that may guide and enhance psychotherapy. Empathic attunement to patients is equally relevant for psychopharmacologic interventions and psychotherapy, and for all patient-doctor relationships. (HARV REV PSYCHIATRY 2011;19:162–174.)

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Biomarkers are biologically derived indicators that can predict the development of a disorder, aid diagnosis, predict the course or outcome of a condition, or be used to tailor individual treatments for specific disorders.[1] They can be applied to psychotherapy, a treatment that is just as strongly rooted in brain plasticity as psychopharmacologic interventions.[2] Psychotherapy changes brain function, and as in other areas of psychiatry, the neural correlates of psychotherapy can potentially be informative in predicting treatment response. But research on psychotherapy and empathy also tells us that the relationship between patient and therapist reflects an underlying biology and thus that the relationship itself can be characterized by markers that can potentially be used to improve treatment. In this article, physiological and neurobiological underpinnings of psychotherapy and the psychotherapeutic relationship will be explored, with suggestions for enhancing detection of

somatic and affective clues in patient and therapist that may deepen empathy and physiological attunement in the psychotherapy dyad.

PSYCHOTHERAPY AND THE BRAIN

Psychotherapy Is Associated with Biomarkers of Physiological Changes in the Patient

As reviewed elsewhere[3–5] but discussed further here, studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have found that psychotherapy has measurable effects on the brain. Moreover, PET studies have shown that the changes in brain activity from psychotherapy are similar to those from pharmacotherapy. For example, in obsessive-compulsive disorder (OCD), pharmacotherapy and psychotherapy were associated with a reduction in metabolic activity in the caudate nucleus,[6] and in phobic disorders, cognitive-behavioral psychotherapy (CBT) and pharmacotherapy demonstrated significantly reduced activity in limbic and paralimbic regions.[7] Electroencephalography (EEG) and neuroimaging studies have revealed effects of psychotherapy on brain function across a range of psychiatric disorders.[8] Further psychotherapy biomarker research is needed to continue to elucidate patterns for treatment selection and to tailor individual treatments for specific disorders.

Treatment Response to Psychotherapy Is Associated with Markers of Brain Physiology

Whereas psychopharmacological interventions have been a primary focus for biomarker research, a comprehensive review indicated a great potential for neuroscientific tools to be used in psychosocial treatments to predict treatment response.[4] These changes in brain physiology can be harnessed not only to predict treatment response, but also to indicate incremental improvement. Thase and colleagues[9] examined the relationship between EEG sleep profiles and response to interpersonal therapy (IPT) for depression and found that subjects with abnormal sleep profiles had poorer clinical outcomes than subjects with more normal sleep profiles. In an earlier study they found that CBT and tricyclic antidepressants may share several common EEG sleep correlates of treatment responsiveness.[10] In patients with OCD, investigators found a reduction in glucose metabolism in the right caudate nucleus in treatment responders following a course of CBT; furthermore, those patients who responded most favorably to CBT not only exhibited a more pronounced reduction in glucose metabolism, but also demonstrated an uncoupling of hyperactivity in the right caudate, orbitofrontal cortex (OFC), and thalamus.[6] In major depressive disorder (MDD), decreases in dorsal and ventral prefrontal cortical metabolism were found in response to IPT and pharmacotherapy.[11] Another MDD study using single photon emission computed tomography compared regional cerebral blood flow in patients who received IPT or venlafaxine. This study found clinical improvement in both groups associated with increased blood flow in the right basal ganglia, though the IPT group also exhibited an increase in right posterior cingulate activity.[12] These studies illustrate the potential for biomarkers to track the course of treatment response and to create opportunities for clinicians to refine personalized treatment approaches.

Reports on physiological changes occurring in patients during psychotherapy date back as early as the 1930s, when affective changes during psychoanalysis were correlated with galvanic skin response (or what is commonly referred to as skin conductance [SC] or electrodermal response) and heart rate.[13] Since then, numerous investigators have reported physiological changes in patients during psychotherapy, including changes in finger temperature,[14] muscle tension,[15] respiration rate,[16] and SC.[17] Increases in SC are correlated with both sympathetic activation and emotional arousal. In addition, reductions in SC have been correlated with patient mastery and control over threatening material, and conversely, increases in SC have been correlated with decreased sense of mastery.[18] These studies support the hypothesis that affective intensity during psychotherapy (especially negative affect) is associated with greater autonomic arousal than calm affect states representing greater mastery or sense of control.[19]

NEUROPHYSIOLOGICAL CORRELATES OF THE PATIENT-CLINICIAN *RELATIONSHIP A*RE RELEVANT TO TREATMENT OUTCOMES

Research on psychotherapy and empathy reveal neurophysiological correlates of the patient-therapist relationship that may also be salient for treatment outcomes. Empirical evidence supports a significant relationship between patient measures of perceived therapist empathy and outcome in psychodynamic and cognitive-behavioral therapies over the past several decades.[20–23] The theoretical literature defines empathy as the ability to both cognitively and affectively understand and respond to the unique emotional experience of another person, which entails a degree of sharing that person's emotional state and includes taking the perspective of the other person.[24] Experimental psychologists refer to three necessary qualities ascribed to empathy: (1) *knowing* what another person is feeling (empathic accuracy); (2) *feeling* what another person is feeling; and (3) *responding compassionately* to another person's distress.[25] A critical review also found that lack of therapist empathy was

the best predictor for negative outcomes in psychotherapy.[26] Because empathy is so strongly correlated with outcomes in psychotherapy, neurophysiological correlates of the patient-clinician relationship are important to consider in research on treatment outcomes and biomarkers.

The Neurobiology of Empathy

A specialized class of neurons called "mirror neurons" provided the first neurobiological basis for translating motor actions that an individual observes in others into internal representations in the observer's brain, facilitating understanding of other persons' actions.[27] These neurons, found in the premotor cortex and inferior parietal cortex, are activated when a primate *performs* an action and also when it *observes* the same action performed by another primate. Early mirror neuron research led to prolific MRI investigations of "self versus other" brain mechanisms that facilitate empathic understanding of one person's experiences by another. Initial claims that mirror neurons were responsible for a wide range of abilities, such as language acquisition and altruism, have recently been challenged by some investigators.[28,29] Current research is identifying similar hemodynamic changes in the anterior cingulate cortex (ACC) and other neuroanatomical structures of "self" and "other" that facilitate understanding of other persons' experience and that are activated both when subjects experience, and when they observe, touch and somatic sensations,[30] pain,[31,32] and emotions such as disgust.[33]

The central neuroanatomical structures identified in neuroimaging studies of empathy, particularly the ACC, significantly overlap with the brain structures that control fluctuations in SC, with the consequence that changes in SC provide a way of tracking changes in those brain structures. SC varies with the skin's moisture level, determined by release of sweat from the eccrine glands. Since those glands are controlled by the sympathetic nervous system, SC can be used as an indication of psychological or physiological arousal.[34] Converging clinical and neuroimaging findings suggest that the ACC mediates modulation of emotion, cognition, sensation, and movement; it also mobilizes appropriate responses to internal and external stimuli, integrates emotional-cognitive responses, and coordinates motor preparation and conflict monitoring. The ACC carries out these functions by activating somatic states that focus attention on internal and external demands and that motivate appropriate action through its projections to autonomic, visceromotor, and endocrine systems[35] (Figure 1).

A principal function of the ACC is the regulation of bodily states of arousal to meet concurrent behavioral demands that are presented by social contexts with either threatening or benign stimuli. The ACC, OFC, and amygdala are

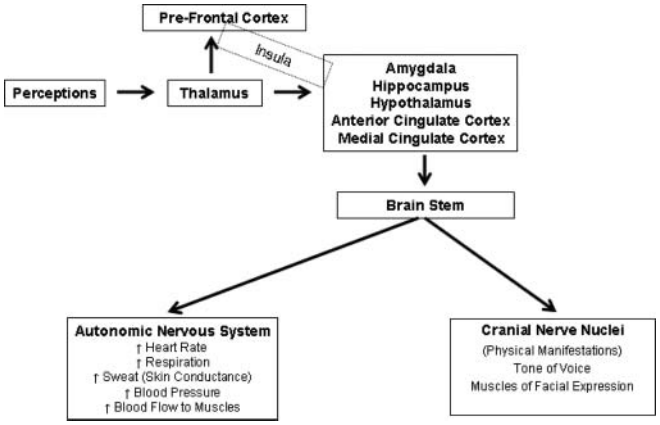

Figure 1. Physiological and physical responses in emotion

involved in decoding facial expression, direction of gaze, and other nonverbal behaviors.[36] The ACC plays a major role in coordinating emotional appraisals and autonomic arousal processes with cognitive and social perceptions, such as *observing others* experiencing pain and *experiencing self-pain*. It projects directly to neural structures implicated in empathy. One fMRI study demonstrated a link between observing others' pain and the response of the observer's motor system, suggesting that part of the empathic response (like that of a response to pain itself) consists of overt motor actions such as motor preparedness for approach or avoidance—for example, flinching when seeing another person cut his finger.[37] Other reports show that the anterior insula is activated both when experiencing pain and when observing others in pain, suggesting a shared neural circuitry for the experience of pain and for empathic response to other's pain.[38–40]

Neuroimaging studies have identified neural correlates of empathy by identifying brain activity associated with the imitation and observation of different facial expressions of emotion.[41] A novel MRI study also demonstrated that empathic responses can be elicited automatically without emotional cues by merely presenting an arbitrary cue (such as a colored light) that signals the feeling state of another person. In a groundbreaking study of 16 couples, the female partners received a neutral signal that indicated that their spouses were receiving painful electric shocks to their hands. Simply observing this cue resulted in the activation of most, though not all, of a well-defined pain matrix in the female partners' brains.[38] This neuroimaging study was the first to demonstrate that when people say, "I feel your pain," it is not just a figure of speech. The authors reported a direct correlation between activity in the observers' ACC and scores on empathy scales.[31]

This research supports the notion that the therapist's observation of patient signals (such as playing with hair, clearing the throat, fidgeting, or other voluntary signals) may enhance appreciation for emotional states, even if the facial

expression of the patient does not reveal emotions. Empathy is an emotional, social, and cognitive process that allows an observer to understand and feel another's emotions by neural mapping that occurs in the observer's brain. Empathic individuals appear to show a nonconscious motor mimicry of facial expressions, postures, and mannerisms of others to a greater extent than less empathic individuals.[41–44] Action representations of others' facial and bodily movements appear to involve the ACC and the insula, which together form a "salience network" that segregates the most relevant internal and extra-personal stimuli in order to guide behavior. The anterior and posterior insula appear to interact as a hub, to integrate salient stimuli and events with visceral and autonomic nervous system activity. Together they help to generate a heightened physiological awareness of salient stimuli and to generate appropriate behavioral responses.[45]

Empathy and Skin Conductance Fluctuations

The first study directly investigating perceived empathy and simultaneous SC fluctuations was conducted in nonclinical, student-counselor dyads.[46] The authors found that the frequency of SC peaks between clients and counselors was positively correlated with student ratings of counselors' empathy. Subsequent studies have demonstrated support for a physiological basis of empathy. Wiesenfeld[47] measured SC responses of women watching video clips of infants expressing a range of emotions. High-empathy females had larger SC responses and matched the infants' facial expressions more often than low-empathy females. Levenson and Reuf[25] found that subjects' ratings of negative emotion when watching a video clip of a distressed married couple were highest when the subject and the couple had high levels of physiologic concordance. Marci and Orr[48] found low levels of perceived empathy and low SC concordance in patients interviewed when high emotional distance was created by an interviewer who avoided making eye contact. These studies suggest that empathy and physiological concordance occur in dyadic settings that do not necessarily have a therapy focus, and that they may represent critical factors in caring human relationships.

The evidence for the significance of patient perceptions of therapist empathy during psychotherapeutic treatments[20,22] has led to investigations into the biological correlates of empathy. The rationale for using biological markers during psychotherapy is that greater awareness of simultaneous autonomic responses may assist in deepening the process of psychotherapy. Neuroimaging and psychophysiology research has revealed significant insights into underlying mechanisms of empathy and interpersonal processes that may affect the patient-doctor relationship.[25] Humans have sophisticated perceptions of others' behavior that elicits feelings of social comfort or potential danger—feelings that may be especially acute in the patient-psychotherapist relationship. The autonomic nervous system is linked to the affective experiences of self and other that motivate approach and avoidance behaviors based on systems of social engagement. Therefore, exquisite sensitivity to autonomic nervous system activation may enhance therapist and patient awareness of real or perceived interpersonal threats, fantasies, thoughts, conflicts, impulses or emotions.[19]

PHYSIOLOGY BETWEEN PATIENT AND CLINICIAN

The interface of psychological and physiological variables during psychotherapy has been the subject of investigation for decades. This interface has historically been assessed using physiological measurements of autonomic nervous system activity, including heart rate, blood pressure, respiration rate, body temperature, gastric motility, muscle tension, EEG, and SC. The last of these is highly sensitive to emotional states occurring between two people, including anger, fear, sexual arousal, and the startle response.[19] According to Porges's polyvagal theory,[49] the neurological basis of social engagement is evolutionarily linked to the autonomic nervous system and how it relays emotional experiences. Porges proposes three parts of the autonomic nervous system, including (1) vagal visceral unmyelinated afferents that decrease metabolism in response to environmental threats and that contribute to somatic feelings associated with emotional distress, including behavioral immobilization seen in certain animals feigning death; (2) the sympathetic nervous system, which increases heart rate and motor activity for the "fight or flight" response; and (3) the parasympathetic nervous system involving the myelinated vagus nerve regulating cardiac activity with discriminating responsiveness to social approach or avoidance by downregulating cardiovagal tone. The myelinated vagus nerve is also linked to adaptive social behavior by relay mechanisms to the cranial nerves that regulate facial expression, vocalizations, and listening. These three parts of the autonomic nervous system are all critical components of interpersonal engagement.

Ax[50] suggested that psychotherapist empathy might be thought of as "an autonomic nervous system state that tends to simulate that of another person," and his research revealed linkages between the physiological responses of psychotherapist and patient. DiMascio[51] found that patient and therapist heart rates varied together "in concordance" during some moments in psychotherapy and oppositely in "discordance" during other moments in psychotherapy. These early studies provided indirect support for a

physiological component to "empathic relatedness" during psychotherapy.[52,53]

Patient-Clinician Skin Conductance Concordance

Another group of studies examined physiological states between patient and therapist during psychotherapy where the autonomic arousal of both members of the dyad was simultaneously measured. Early studies using measures of SC and heart rate suggested that patients and therapists were highly reactive to each other.[54] As noted above, these studies showed that the physiologic responses of patients and therapists varied together and oppositely at different points in therapy sessions.[52] This research showed a relationship between concurrent SC fluctuations (as a representation of autonomic activity) and perceived empathy in dyadic interactions.[19]

Recent research at Massachusetts General Hospital of 20 patient-therapist dyads specifically investigated the relationship between SC and perception of therapist empathy during psychotherapy in videotaped sessions where simultaneous measures of patient and therapist SC were obtained. The results demonstrated a significant correlation between levels of physiological SC concordance and patient-perceived empathy as measured by the Empathic Understanding Scale ($r = 0.47$, $p = 0.03$).[55] The results support a biological model of physiological concordance and perceived patient empathy during psychotherapy. The moment-to-moment physiological concordance suggests that there is an unconscious central nervous system mapping of one person's experience onto the other's that is mediating a physiological response; neuroimaging research supports this claim.[35]

In SC tracings, physiological *concordance* between a patient and therapist appears as a closely matched image of their respective sympathetic nervous system activity. Rather than looking for "causality" of one person's physiology affecting the other, it is better conceptualized as epochs of physiological synchrony that appear frequently or infrequently during a session, or not at all. The relationship to the degree of therapist empathy is made by correlating responses on an empathy rating scale and the number of epochs of physiological concordance. For examples of SC tracings, see Marci and colleagues (2007)[55] and Marci & Riess (2005).[56]

The clinical relevance of SC as a tool for measuring patient-therapist concordance is illustrated in the following case example,[56] which also shows that some patients may benefit both emotionally and clinically from direct observation of their own SC tracings.

Case Study

A psychodynamically oriented psychiatrist (the present author was the therapist) and her patient were enrolled in a study where both therapist and patient received SC monitoring during a videotaped psychotherapy session. The SC tracings demonstrated a high level of physiological concordance, which matched the patient's assessment of the therapist as empathic on the empathy questionnaire for the monitored session.[56] Measurements of SC also revealed, however, a hidden state of autonomic arousal in this obese patient, who had learned to mask her anxious feelings since childhood as a way of maintaining a connection with her overburdened mother.[58] In sharp contrast to the rest of the session, there were a few moments in which the patient's SC spiked to three times that of the therapist's, even though the patient showed no overt signs of anxiety or autonomic activation. In this session with her psychiatrist, the patient had repeated her early pattern of concealing her anxiety from her mother.

The episodes of discrepancy between the SC in the therapy pair led the therapist to ask the patient if she was interested in seeing the results and in discussing the possible meanings of the findings. The decision to introduce this question was based on the formulation of the patient's case, along with the patient's expressed interest in how the findings of the study could help others and herself. Sharing such data must be weighed carefully in relation to specific indications and contraindications. For example, paranoid or obsessive patients may find this type of information threatening, negative, or critical in nature.[19]

When the patient examined the tracings, she commented, "It's as if I'm seeing an 'X-ray' of my psyche." The patient had been the most agreeable child in a large family, with siblings who had physical disabilities. She had learned to conceal her own anxious states in the service of acting as her mother's emotional caretaker and confidant. The patient used food to soothe herself, became obese, and subsequently became the object of her mother's ridicule, which ultimately led her to seek psychotherapy to resolve this painful double-bind.

The therapy dyad together examined their simultaneous autonomic arousal levels gathered from time-series analysis. The physiological data validated the patient's emotional experience and allowed the therapist to gain deeper empathy for her patient. Importantly, the data also led the therapist to examine the videotape of the monitored session for indications of subtle clues of somatic markers of her patient's anxiety. The high peaks of autonomic arousal corresponded to physical changes in facial expression and skin tone (slight flushing), averted eye contact, fingers raised to hair, and a throaty chortle. These physical signs served as markers for detecting subtle signs of anxiety that were not verbally expressed but that matched the spikes on the SC data. These observations of the patient's unique physical manifestations of her anxiety led to a deeper level of therapist insight into how this patient revealed her anxiety, and fostered greater empathy for this patient's suffering.

During the next year of psychotherapy the patient-therapist relationship deepened to a new level of emotional

connection and compassion. For the first time, the patient was able to talk about her shame regarding her weight and lack of exercise. Insight into her habitual sedentary lifestyle and her use of food to soothe herself led to more adaptive behaviors to manage her anxiety. She hired an exercise trainer and became more comfortable revealing her anxiety and vulnerability to her therapist. Most remarkably, the patient lost 40 pounds in the next year; the first time this patient had ever lost weight. The therapist's attunement to physical signals of emotional pain and anxiety increased her empathy and, in turn, helped her patient achieve her therapy goals.

Discussion. This case began by presenting a session where a high overall degree of physiological concordance was present, with high ratings of perceived therapist empathy. The areas of SC discordance illuminated areas of anxiety that had been hidden from the therapist. One could mistakenly conclude that an optimal session would depict full physiological concordance. However, too much concordance could mean that the therapist was not addressing disconnections or employing therapeutic tools (such as clarification, interpretation, and confrontation) necessary to improve the patient's ability to function in relationships. Kohut,[57] in his description of the "optimal frustrations" inherent in every dyadic relationship, theorized that such discordance offers opportunities for exploration, repair, and transmuting internalizations—leading to a stronger psychic structure. In this case the discordant SC tracing provided a window to explore less obvious, but ultimately important, causes of the patient's anxiety, enabling her to lose significant weight. Examination of the patient's defenses of masking her anxiety and vulnerability led to greater empathy and more relational solutions to manage her anxiety. The case demonstrates the potential of a biological marker of physiological activity to enhance attention to clinical manifestations of emotions and to improve outcomes in psychotherapy. It also provides evidence that subtle physical signs or mannerisms manifested during psychotherapy may be markers for internal, but undisclosed, affects such as anxiety. Careful therapist attunement to these signs may enhance and deepen psychotherapy if explored.

PHYSIOLOGICAL SIGNS OF EMOTION CAN SERVE AS BIOMARKERS IN CLINICAL PRACTICE

The theoretical bases for many models of psychotherapy have historically focused on verbal exchanges intended to foster modifications in human feelings, cognitions, attitudes, and behaviors.[58] While common factors such as empathy, trust, respect, support, and openness are considered critical features of psychotherapy, biological markers for these factors have received relatively little attention despite their crucial role in forming a therapeutic alliance. Empathy is necessary, but not sufficient, for forming the therapeutic alliance, which has been defined as "the persistent and ultimately predictable and expectable experience on the part of the patient of the steady, reliable, reasonable, fair, kind, tolerant, non-judgmental, but also non-corruptible attitude of the analyst."[59] According to Havens, "Alliance formation is the first order of clinical business,"[60] and the strength of the therapeutic alliance is significantly and consistently related to psychotherapeutic and medical outcomes.[61–65]

The theoretical approaches of three widely practiced psychotherapies—psychodynamic, cognitive-behavioral, and interpersonal—suggest that while attention to emotions and affects is integral to each of these therapies, explicit focus on somatic manifestations of emotions is not generally considered critically necessary for positive outcomes. These conventional therapies are, indeed, frequently sought in response to somatic sensations signaling anxiety, panic, flashbacks, and other signs of somatic distress, but specific training in detection, management, and interpretation of the *physical* manifestations of emotions is not an integral part of most psychotherapy curricula. Modalities that explicitly emphasize attention to the body in order to understand emotional states include biofeedback,[66] mindful meditation,[67] hypnosis,[68] the mind-body relaxation response,[69] and internal family systems therapy.[70] These modalities are sometimes utilized in conjunction with conventional therapies to help patients attend specifically to somatic sensations.

Whereas verbal exchange is essential for communicating thoughts and feelings in psychotherapy, the renowned analyst Elvin Semrad was well known for his interest in identifying biological markers indicating where his patients experienced their emotions. Semrad's therapeutic statements evincing his interest in making connections between expressed emotions and their felt location in the body include the following: "This is what makes the difference, the *tissues* of the person involved, not the fancy thought upstairs"; "I respect the autonomic nervous system to show feelings like I respect few other things"; and "Acknowledging the feelings and reality of her body is overwhelming her mind with guilt."[71] Semrad was known to explicitly ask his patients, "Where do you feel your pain?" (Briggin I, personal communication).

Studies of dyadic and group interactions during psychotherapy have demonstrated that the behavior of both the patient and the therapist influence one another physiologically in a powerful way. With psychological rapport, autonomic activity is reduced in both patient and therapist, but with conflict and negative interaction, autonomic activity is heightened in both.[72,73] The most important conclusion from these studies is that physiological synchrony

between patient and therapist occurs when the therapist is accurately perceiving and empathizing with the patient. Physiological changes during therapy do not occur in isolation. They reflect, instead, moment-to-moment interactions within the therapy pair—serving as an exquisitely tuned index of therapeutic alliance.[19] New teaching tools are needed to augment clinician awareness of these moment-to-moment interactions within a therapy dyad, enabling the clinician to garner as much clinically relevant information as possible. A shift to include the physiological manifestations of emotions—and not just verbal accounts and interactions—may enhance diagnostic accuracy of states of anxiety, fear, threat, disengagement, equanimity, or joy.

These studies indicate that affective arousal during psychotherapy is associated with increased autonomic nervous system activation, whereas affective equanimity is correlated with diminished autonomic and voluntary nervous system activity.[19] Emotions are physiologically grounded in the autonomic nervous system, and they affect several target organs to enhance individual and species survival via complex neural, hormonal, and physiological processes.[74] Familiar somatic descriptions of negative emotions, such as feeling "heavy hearted, "sick to my stomach," "all choked up," "my head is exploding," having "butterflies in my stomach," or "heart-pounding terror," and of positive emotions, such as feeling "light hearted" and "floating on air," suggest that humans feel their emotions in their bodies. Clinician attention to these feelings may deepen the therapeutic alliance and process.

Detection of Physical and Physiological Signs of Emotion with the E.M.P.A.T.H.Y. Mnemonic

The critical need to improve empathy in all areas of medicine must be addressed with specific training protocols.[75] Enhanced detection of physical markers of emotion can assist clinicians in becoming more attuned to patients' needs. Biomarkers have been defined as "a specific physical trait used to measure or indicate the effects or progress of a disease, illness, or condition."[76] Many physical signals and signs of emotion are frequently overlooked in the practice of psychiatry, including psychotherapy. Not only can these physical manifestations be important indicators of what is happening with the patient, but they may also provide a window into underlying neurobiology, thereby playing a role similar to that of conventional biomarkers. These signals and signs can be organized using a novel mnemonic device, E.M.P.A.T.H.Y.

The mnemonic E.M.P.A.T.H.Y. focuses attention on specific neural correlates of empathy that are grounded in the neuroscience and attachment literature. They include E for making meaningful *eye contact*, M for decoding *muscles of facial expression*, P for *posture* decoding, A for *affect* perception, T for *tone of voice*, H for *hearing* and *healing* the patient, and Y for *your response*, which asks doctors to take notice of their own emotional response to the patient. Attention to these behaviors and responses (as in measuring SC) can serve as phenotypes of a sort, in that they can reflect meaningful neurobiological activity and can also be considered as a gateway to exploring critical, but less obvious, manifestations of patients' symptoms. In a recent pilot study in which resident physicians were trained with the E.M.P.A.T.H.Y. model, the residents demonstrated statistically significant increases on scales of self-reported empathy and in scores assessing knowledge of the neurobiology of empathy, along with positive trends on scales of patients' perception of physician empathy and communication skills.[77] The E.M.P.A.T.H.Y. approach may enhance therapeutic practices common to all models of psychotherapy and to the patient-doctor relationship in general. At the pedagogical level, E.M.P.A.T.H.Y.'s novel review of the physical manifestations of emotion could be included in the traditional "review of systems," resulting in a more comprehensive patient interview. This process may encourage upregulation of empathy in the patient-doctor relationship, both at the critical time of forming an alliance with a new or prospective patient and in the continuing work with existing patients. More generally, the use of E.M.P.A.T.H.Y. in the review of systems could be implemented in all specialties, as it is a critical component of humanism in medicine.[75] Its use in reviewing the physical manifestations of emotions could also be incorporated into research on psychotherapy process and outcomes to determine if enhanced awareness of biological markers facilitates not only empathy, but also discussions of possible undisclosed emotions. The next section reviews the biological correlates of each component of the E.M.P.A.T.H.Y. mnemonic.

BIOLOGICAL CORRELATES OF E.M.P.A.T.H.Y.

E = Eye contact

The human face provides a wealth of information about expressed emotion and is a primary instrument for social communication. For example, eye contact is usually the first signal that one person has been noticed by another person.[78] In an fMRI study of the effects of eye contact on amygdala sensitivity to angry and fearful faces, gaze direction was found to differentially modulate the perception of angry and fearful facial displays.[79] Angry faces with *direct* gaze (unambiguous threat) and fearful faces with *averted* gaze (indicating the location of the environmental threat) were recognized more quickly and accurately, whereas angry faces with averted gaze (ambiguous threat) and fearful faces with direct eye contact (also an ambiguous threat)

elicited stronger responses in the left amygdala. The importance of eye contact in the patient-therapist relationship underscores the necessity of making eye contact that is perceived as safe to the patient. When clinicians avert their gaze while taking extensive notes or while entering data on their computers (without explaining what they are doing), they risk alienating their patients. Patients may experience signs of disengagement conveyed by an averted face and poor eye contact as disapproval, dislike, or lack of interest.

Interestingly, neural correlates of eye-gaze processing have been found to be abnormal in children with autism. Neuroimaging and electrophysiological studies have shown that in normal controls, eye contact is processed in the superior temporal sulcus and the amygdala,[80] and that brain activation patterns in these areas are affected by whether changes in gaze are congruent or incongruent with neurological responses to visual emotional targets, such as facial expression. While individuals with autism show neural activity in similar regions as normal individuals (amygdala and superior temporal sulcus), modulation of eye contact to respond to new targets in different contexts is reduced.[81] This research indicates the importance of gaze processing for emotional connection.

M = Muscles of facial expression

The cranial nerves that regulate social engagement through facial expression, vocal and verbal communication, and affective experiences are connected neuroanatomically to the portion of the vagus nerve that regulates cardiac contractions. When a person sees a safe or trustworthy facial expression, a neural circuit that projects from the temporal cortex to the amygdala inhibits limbic defensive fight, flight, or freeze behaviors.[74] In patient-therapist encounters, subtle micro-expressions of the face[82] may be especially threatening to the patient due to the unequal status of the relationship, and the patient's internal regulatory processes may promote withholding of particular affects and information. Members of the same species who are in unequal positions of power are especially sensitive to perceived facial threats, and when communication is inhibited, all parties are at risk for interpersonal misperceptions.[83] Clinicians should be aware of the negative effects that blank expressions can have on patients. Cohn's research[83] demonstrates that the unresponsive face of a caregiver can produce the same behavioral and physiological responses as in still-face paradigms—which are emotionally disorganizing and predict insecure attachment as early as six months of age.

Paul Ekman[84] concluded that humans have seven universal emotions that are manifested in facial expressions: sadness, anger, fear, surprise, happiness, disgust, and contempt. And since microexpressions of emotions are generally displayed for only 0.25 second, the untrained eye can easily miss important information conveyed by a person's fleeting facial expression.[84] Neuroimaging studies have explored the neural correlates of empathic experience by comparing brain activity associated with the observation versus imitation of pictures showing different facial expressions of emotion.[41] One study measured neural responses elicited by subjects watching videos of faces with disgusted expressions, and compared those results to neural responses induced by the same subjects smelling aversive odors.[33] Activity in the insular cortex was elicited both by smelling a disgusting smell and by seeing a facial expression for disgust.[33] Moreover, if the facial expression is *imitated* by the observer, the neural circuits are stronger than in the case of observation alone.[41]

Investigators using electromyography found that automatic mimicry of facial expressions of happiness or anger is greater in high-empathy versus low-empathy observers. The differences between the groups in emotional empathy were related to differences in automatic somatic reactions to facial stimuli rather than to differences in their conscious interpretation of the emotional situation.[85,86] Saarela and colleagues [87] demonstrated that humans can detect intensity of pain from another's face. Increased activation was observed in subjects' brain regions that correlated with the intensity of observed pain and also with subjects' self-rated empathy. Thus, the intersubjective representation of pain in the human brain may be more detailed than previously thought.[87]

P = Posture

Darwin suggested that the evolutionary purpose of emotions is to predispose humans to act adaptively and that characteristic body movements and postures are associated with emotional states that have evolved to promote survival.[88] Body movements may be just as important as facial expressions for understanding the neurobiology and meaning of emotional behaviors.[39] In the clinical case described earlier, the patient's motor movements when playing with her hair coincided with spikes in her SC tracings and therefore served as a motor and postural sign of her anxiety—one that the therapist began to recognize after examining the SC data. Some of the same brain areas involved in the perception of facial expressions—the amygdala, fusiform cortex, prefrontal cortex, OFC, medial frontal cortex, superior temporal sulcus, and somatosensory cortex[89,90]—play a role in perceiving body movements. An important finding is that observing bodily postures activates two well-known areas that are predominantly associated with processing facial expressions (the inferior occipital gyrus and middle fusiform gyrus). The activation in facial-expression-related areas may result from context-specific perceptual mechanisms

that fill in the missing face information. There appears to be a striking similarity in visual encoding between faces and body postures.[91]

A 2004 fMRI study found that viewing fearful whole-body expressions, as contrasted with emotionally neutral postures, produced high activity in areas that are known to specifically process emotional information (amygdala, OFC, posterior cingulate, anterior insula, retrosplenial cortex, and nucleus accumbens). Conversely, comparisons of happy bodily expressions with neutral ones yielded increased activity only in visual areas. These finding suggest that dominant body postures, such as standing over patients, may be perceived as potentially threatening.

Recent neurobiological models of empathy suggest that motor, perceptual, and emotional states of one individual activate corresponding representations in another individual who is observing those states.[92–95] In primate studies, single-cell recordings show that premotor, or mirror, neurons become activated both while executing a given action and while observing the same action performed by another primate. This parallel activation may account for the unconscious "mirroring" that takes place when two individuals seated opposite one another find themselves assuming the identical posture. Shared motor responses are also seen when one person is injured (such as getting a hand slammed in a car door) and both the participant and the observer react by flinching. Similar examples of motor activity that signals pain or anxiety, such as the touching of hair in the case example, can be understood as motor manifestations (external markers) of internal pain and may even be unconsciously shared or mirrored by observers.[37,39] Similar to facial expressions, the manipulation of posture has been used to produce feelings of anger, sadness, disgust, and fear in the observer.[96–98]

A = Affect

Affect refers to the emotion conveyed by the patient that is consciously observed by the clinician. Emotional appraisal of patient affects allows therapists to orient themselves to the particular emotion of the session. Neural correlates of affect include perceptions routed through the thalamus, ACC, amygdala, and OFC, all of which project to the insula, which then relays emotional contents to limbic areas.[38–41] By mirroring changes in patients' affect by verbal and facial expression, clinicians may facilitate empathy; MRI studies show that neural circuit activation is stronger in observers when others' facial expressions are imitated by the observers than by simple observation alone.[41] The research by Bowlby[99] and Ainsworth[100] also provides support for a human motivation for affective engagement; clinicians must be aware of the potential negative effect that a lack of affective expression might have on their patients.

T = Tone of voice

Human beings are exquisitely sensitive to variations in tone of voice. Hearing helps humans to understand actions and motivations of others via neural mechanisms for shared experiences for sounds.[101] Research by Ambady[102]—using content-filtered slices of conversations between surgeons and patients, preserving only intonation, pitch, and rhythm but erasing the content—showed that judges could accurately predict which surgeons had been sued and which ones had not. The affective tone of a therapy session may thus be set more by tone of voice than the words spoken. Changes in a patient's tone of voice and how a clinician responds may determine that patient's perception of the therapist's empathy and attunement. Aggressive tones of anger and rage versus gentle, soothing sounds have been shown to induce the identical range of emotional feelings in the listener when passages were read using the pace, rhythm, and pitch of these emotions.[103–105]

H = Hearing/healing

"What am I hearing, and what would be healing for this patient?" This item in the mnemonic asks the clinician to be mindful of what is being transmitted by the patient's narrative and also what requires an empathic response. This question assesses the overall state of the patient. It may mean responding to an especially intense affect, to a situation in the patient's life, or to something that has happened to a loved one that calls for the expression of compassion and empathy. It could also be a rupture in the patient-therapist relationship that needs attention. Given the neural correlates of hearing[103–105] and the shared neurobiology of pain and painful facial expressions,[38,41] an empathic response to the patient is likely to be experienced as supportive and healing. A compassionate nod, a gentle tone of voice, can make the emotional difference in an office visit.

Y = Your response

Dimascio[51] was the first to demonstrate the importance of the shared autonomic physiological response between patient and therapist in psychotherapy. Many studies support the notion that empathy has a physiological substrate that provides an internal experience that is shared between people. The psychoanalytic concept of "projective identification"[106] is a process whereby patients' unexpressed emotions are experienced by the clinician as the first signal of what the patient is feeling. Projective identification may occur by a process in which patients' feelings are projected onto clinicians through explicit and implicit physical and physiological cues that are both consciously and

unconsciously perceived by the therapist. The result is an internal representation of patient affect that is introjected and experienced by the clinician.

Neuroimaging studies indicate that these projections are decoded by the action of mirror neurons that identify subtle cues and micro-expressions[85] that are below the threshold of consciousness but perceived by the observer. Many clinicians are aware of dreading certain patient encounters because of the negative affects they associate with those patients. By developing "critical curiosity,"[67] physicians may be able to identify the affects that the patients engender within themselves. Negative feelings such as guilt, anger, or disrespect *elicited in* the physician may be the precise feeling that the patient is experiencing but not disclosing. When clinicians are able to reflect on their own feelings with curiosity and do not automatically react to what is being projected on to them, a space for new possibilities is created. The capacity to respond with what would be helpful to the patient, rather than with an unexamined emotional reaction, is an ideal that requires clinician self-reflection and self-regulation.

CONCLUSION

Biomarker research is being conducted at all levels of psychiatry and psychotherapy. While this research is unfolding, clinicians must keep in mind that various observable physical markers that reflect underlying neurobiology can be put into practice immediately. In light of the data supporting physiological signs of emotion, more emphasis must be placed on detecting physiologically based markers of emotion to enhance clinical effectiveness. Clinicians must be trained to detect subtle signs of emotions.[75,107] This emphasis is needed in psychiatric, medical, and psychological training curricula, in parallel with ongoing biomarker research, in order to raise awareness of the connection between mind and body—and thereby enhance the process of psychotherapy.

Prospective studies are needed to provide algorithms for tailored individualized treatment plans for psychotherapeutic interventions, allowing clinicians and patients to avoid lengthy and costly "trial and error" approaches.[4] A major shortcoming of psychotherapy is that it is currently difficult to predict which treatment is best for which patient, and treatment failure may not become apparent until weeks, months, or even years have passed. Measures of physiological concordance and discordance in psychotherapy, along with the careful examination of subtle signs of affects, may become increasingly important for identifying signals of treatment impasses or failures.

Continued biomarker research is needed in order to yield individualized, biologically based data to improve selection, effectiveness, and efficiency of psychosocial treatments. The wide frontier of genetics research promises to steer individuals with specific genetic sequences to the most effective psychotherapeutic and psychopharmacological treatments. In the future, psychotherapy will likely be increasingly guided by advances in neuroscience and biomarker research—the necessary scientific foundation for clinical practice. Against that background of scientific knowledge, however, the clinician's mandate will always include astute clinical observation of the patient. There is no substitute for looking at, hearing, experiencing, and identifying the patient's clinical presentation, for that is the substance and substrate of empathy in the patient-clinician relationship.

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